Advanced Clinical

INSIGHT BRIEF

Operationalizing Decentralized and Hybrid Clinical Trials: Best Practices for Ensuring a Better Patient and Site Experience

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Introduction

Rising sharply in popularity during the COVID-19 pandemic, decentralized clinical trials (DCTs) have been used to bring components of a clinical trial direct to patients in order to ease the burden of clinical research. The goal of DCTs is to attract more and diverse patients that best represent the population who have the therapeutic indication being studied. This goal continues to be achieved by making it easier for patients to participate in studies from their homes or through technologies rather than in-person participation at a local clinical research site for every visit. Clinical research teams are navigating this emerging way of conducting trials and the industry is incorporating this approach with the hopes of enrolling trials faster with the right profile of diverse patients and more comprehensive and robust clinical data.

Defined as "clinical trials in which some or all of the activities involve direct patient interaction and often require fewer site visits and/or less direct clinician interaction," DCTs build on some remote approaches that have been available for many years. Examples include home health visits, direct-to-patient shipments of supplies and investigational product, and technologies that enable recording of patient-reported outcomes and support patient engagement.

Along with these benefits, DCT elements can raise challenges in study design, conduct and data quality — combined with the need to keep up with regulatory guidance and industry standards across the globe. Study teams, including representatives from the sponsor, CRO, vendors and investigative site personnel, are navigating new ways of conducting research and are working toward aligning responsibilities to support this new environment.

Authored by senior leaders at Advanced Clinical, this white paper examines best practices for operationalizing hybrid and decentralized clinical trials.

DCT Approaches and Implementation

The approach and implementation stages for DCTs are most effective when customized to each trial based on the sponsor's needs as shown in Figure 1. The recommended DCT approach is trial dependent, patient- and caregiver-focused, flexible and modular, and involves technology enablement and training and support for the investigative site and patients. DCTs work best when sponsors are planning and communicating from the beginning and making changes throughout the process, include during pre-protocol feasibility, protocol feasibility, developing the final decentralized strategy, training of teams and sites on new elements required for the study, and supporting and engaging sites and patients.

As with traditional clinical trials, designing global DCTs requires regulations and cultural norms to be considered at all stages in the process.

Since patients are at the heart of clinical trials, understanding the patient journey is an important consideration in developing a DCT strategy. Ideally, this step would be taken prior to designing the protocol as the approach varies widely between indications and populations. Patient journey mapping is a useful approach to help understand the patient contact time frames and patient burden, which will help design studies that minimize patient requirements and barriers to participation, increase patient retention and protocol compliance, and support enrollment diversity plans.[1] This exercise can help inform decisions on DCT components that help attract specific patient populations. Templates for the patient journey are available from the Decentralized Trials and Research Alliance (DTRA).[2]

Figure 1: Approach and implementation stages can be customized to each trial and sponsor

Country	Online Screening and Patient Recruitment	eConsent/ Digital Signature	TeleMedicine	Mobile/Home Visits	Alternate Sites/Metasites
US	Allowed	Allowed	Allowed	Allowed	Allowed
Canada	Allowed	Conditional	Allowed	Allowed	Conditional
Belgium	Unknown	Allowed	Allowed	Allowed	Unknown
Denmark	Allowed	Allowed	Conditional	Allowed	Conditional
France	Unknown	Allowed	Conditional	Allowed	Unknown
Germany	Unknown	Conditional	Allowed	Allowed	Unknown
Italy	Unknown	Allowed	Allowed	Allowed	Unknown
Netherlands	Unknown	Allowed	Allowed	Allowed	Unknown
Poland	Unknown	Conditional	Allowed	Allowed	Unknown
Spain	Unknown	Allowed	Allowed	Allowed	Unknown
United Kingdom	Unknown	Conditional	Allowed	Allowed	Conditional
Australia	Unknown	Allowed	Allowed	Unknown	Conditional
Japan	Allowed	Allowed	Conditional	Allowed	Conditional
China	Unknown	Conditional	Conditional	Allowed	Unknown
South Korea	Unknown	Conditional	Conditional	Conditional	Unknown

Figure 2: Global considerations for DCTs: Key elements by country

Considerations for Global DCTs

As with traditional clinical trials, designing global DCTs requires regulations and cultural norms to be considered at all stages in the process. DTRA has developed a global DCT conduct map showing variations of regulations and cultural norms by country for elements such as online screening, eConsent, telemedicine, home health visits, alternate sites, remote monitoring, eSource, eCOA and others (Figure 2).[3] Standard of care and patient expectations may also vary by country, while some elements are shared across countries, such as the European Union General Data Protection Regulation (GDPR).[1]

Engaging Sites During DCTs

Sites are embracing the implementation of DCT components — some enthusiastically — investing in new technology and platforms, as well as ensuring in-depth training of their teams before study startup and throughout the trial. However, with new providers and new approaches to trial conduct, there have been challenges even for the most enthusiastic sites. Support desks and other backup support methods are essential for new elements — both for the site and for study participants. Communicating accurate and helpful information consistently to patients across sites is something sponsors and CROs will need to consider in study plans. With some sites reporting understaffing and high employee turnover during studies, ensuring this training is implemented at the beginning and throughout the study will be critical to engaging both the sites and study participants.

DCTs often require multiple changes in the way sites conduct trials compared with traditional studies. These include site engagement around elements such as eCOA, eConsent, telemedicine visits, remote site monitoring, traveling and pop-up site staff, patient education on technologies, direct-to-patient investigational product management and logistics, setting up various subcontracts with vendors, and being prepared for "bring your own device" (BYOD) platform and app requirements. The role of the PI and the delegation log criteria are also in question as it relates to home health staff chosen by sponsors on DCTs. This feedback has been given in site forums and directly to the FDA regarding the new draft DCT guidance.

Lessons learned for site interactions include:

- **Feasibility** should include assessment of each site's willingness to utilize DCT components or any ideas they have that would be helpful in the study design
- Some sites have their **own eConsent, home health nurses and telemedicine platforms** and may prefer to use these; how could the sponsor incorporate this option — if at all?
- Support may be needed for **site training with user friendly documentation** and instructions
- **Patient training materials** may need to be provided to the sites, often including a contact list for help desks, site staff, and other vendors such as home health or patient concierge
- **Help desks may be required**, with responsibility clearly allocated between the study coordinator and the help desk
- **Training requirements need to be assessed** for the various CRO and sponsor teams related to responsibilities and technologies
- **Understanding interstate licensing for PIs** may need to be considered for telemedicine visits crossing state lines

Site considerations also include the need to understand any changes in site responsibilities; plan for new responsibilities added by DCT components; determine any impact on site personnel duties; understand and align with relevant local and international regulatory guidance; develop suitable documentation to monitor and demonstrate compliance and develop an adequate infrastructure to meet trial needs over and above those of traditional trials.

Implementing a Coherent Resourcing Strategy

Across the clinical trial ecosystem, the voice of the patient continues to drive change. Enabling patient and caregiver input into clinical development planning is a vital element in minimizing the burden of study participation and optimizing recruitment and retention. Patient engagement involves multiple avenues and approaches, including patient focus groups or surveys, online screening tools, eConsent, texting, ePRO, interactions with patient concierges, direct-to-patient product shipments, patient payments, visit scheduling and reminders.

Patients also need to be trained in reporting of illness or events, use of technologies and devices, and BYOD app requirements.

Lessons learned in patient interactions include:

- A tailored outreach to the desired participant population to obtain feedback is critical to study design, and helps with the goal to enhance inclusivity and plan for diversity
- It is beneficial to minimize the burden of in-person participation for patients and caregivers for many indications, where other indications may find that patients prefer to be seen in person. Each study benefits from:
  - Understanding trends within desired populations
  - Developing flexible trial designs when needed
  - Providing user-friendly interfaces that are intuitive for patient use
  - Clarifying device requirements for studies involving BYOD
  - Delivering consistent patient training (or study coordinator training for patients)
  - Offering support
- Engaging patients throughout the trial can help create better patient retention, such as visit reminders and interactions between visits

Patient Monitoring for DCTs

DCT protocols can be complex, with a range of designs, technologies and data sources. Approaches to patient monitoring need to be resolved as early as possible and follow the most current regulations. Factors that should be considered include: any study requirements for wearables and sensors; home health visits, mobile nurses and phlebotomists; telemedicine visits; uploading of videos and photos; adherence monitoring and ongoing non-visit-related communication.

Lessons learned in patient monitoring include:

- The importance of focusing on protocol design and what data will be utilized
- Ensuring regulatory compliance across guidances
- Device selection and validation of the device
- Planning for patient compliance and engagement
- Data management and integration, including data privacy and security
- Participant training/education
- Site considerations such as delegation logs and training needs
- Planning logistics for direct-to-patient shipments if applicable

Data Connectivity and Integrity

In addition to following technology and DCT guidances, sponsors will need to ensure that integration and data mapping are included in study plans to ensure data integrity and reliability.

DCTs often have more vendors and providers involved than a traditional trial, including home health, technology, telemedicine and more — all with technologies that need to be integrated with other systems such as EDC, safety databases, CTMS, eTMFs and other technologies. How the data are connected, as well as the source of truth and integrity of the data, will need to be outlined in the data management plan. Finally, there are many new players involved in clinical trials involving DCT components, and some of those new players are not accustomed to roles and responsibilities or the regulations that surround clinical trials. Vetting those new providers to ensure they understand the trial process and regulations and integrating them into trial teams is an important role of the sponsor.

The Power of Communication and Alignment

Communication is a vital element in operationalizing DCTs. Even when time pressures exist, it remains essential to document all steps in the processes by function and across providers. Taking the time to comprehensively plan and align is the most important part of the study management process.

All plans, workflows and training materials should be available and will be helpful in engaging sites and training new site staff when they experience turnover. Some project team personnel at the sponsor, the CRO, sites and vendors may not have conducted a DCT and need to be able to ask questions. Understanding new roles within DCTs and building narrative documents and schematics to convey information to stakeholders is helpful to align the entire project team.

Figure 3: Future clinical research industry trends

The Future of the Industry

Current trends are likely to continue, with the patient voice importance present and growing. Regulators are encouraging DCTs and are closely involved, creating new regulations globally. Sites are adapting to DCTs while needing more support from sponsors. In addition, increasing use of decentralized elements is driving a change in the composition of clinical trial teams, adding a need for new analytical roles and educational backgrounds. This may lead to different staffing needs in the future.

Key Takeaways: Recommendations for Sponsors

Recommendations to enable sponsors to implement successful DCTs include:

1. Planning early and remaining flexible: Planning prior to protocol design will allow for options that attract a diverse group of participants from the desired patient population. Selecting and integrating vendors early will help ensure that startup timelines are met, and roles are clear throughout the study.

2. Keeping the patient and caregiver and their journeys in mind at all times and engaging them at the earliest stages for optimal study design and continuing engagement throughout the trial.

3. Being aware of local and global regulatory guidances such as:

   > FDA Draft Guidance on Digital Health Technologies for Remote Data Acquisition in Clinical Investigations[2]
   > FDA Draft Guidance on Decentralized Clinical Trials (DCT)[3]
   > FDA Guidance on Use of Electronic Systems, Electronic Records and Electronic Signatures in Clinical Investigations[4]
   > FDA Draft Guidance on Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials[5]
   > EMA Recommendation Paper on Decentralized Elements in Clinical Trials[6]
   > EMA Guideline on Computerized Systems and Electronic Data in Clinical Trials[7]

4. Deciding on DCT components: Sponsors will need to decide which decentralized components are required for patients and which will be optional. In addition, sponsors will need to decide if sites can use their own staff or systems if they offer the same components. Further, aligning vendors and other stakeholders and defining roles and responsibilities are critical steps to success. Finally, determining who handles patient communication is important, including any needs for help desks and additional support.

5. Understanding how DCT elements impact patient recruitment and enrollment, including site responsibilities, patient concierge, eConsent and patient engagement activities and technologies.

6. Consider scaling your expertise with DCTs by starting with one or two decentralized elements and adding to these as experience is gained. Implementing DCTs can inform and improve future strategies.

7. Training project teams: This includes multiple steps requiring effective change management:

   > Defining expectations for all stakeholders
   > Developing communication and training plans for all stakeholders
   > Creating data connectivity and management plans including schematics for process flow
   > Providing materials to sites to give a consistent explanation of the study and its requirements, as well as materials to use when explaining requirements to patients
   > Ensuring that CRO staff, vendors and internal teams understand their responsibilities and are aligned on how they will work together
   > Defining how tracking and reporting are measured and communicated

8. Reinforcing communications between all relevant stakeholders throughout the trial.

In conclusion, DCTs are here to stay and offer sponsors the opportunity to attract more patients, making clinical trials more patient-centric and with more comprehensive data. However, with the benefits of conducting DCTs also come challenges; therefore, it is important to approach DCTs with additional considerations than you would in a traditional trial. In DCTs, the number of stakeholders increases, processes change, there is often not clarity in roles and responsibilities, regulations are added and the integrity of the trial conduct and the data must remain. When planned correctly, DCTs can be operationalized without compromise. Considering the recommendations above when planning and implementing DCTs will help you ensure success.

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Cheryle has extensive, progressive clinical research experience and is responsible for global strategic planning and tactile operations in project management, clinical monitoring, biometrics, document management and operation quality. She is heavily involved in the transformation of the clinical research industry as it relates to risk management, technical innovation and resource management.

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Caroline is a results-oriented leader with 30 years of clinical research experience. She is responsible for corporate strategy and growth, study optimization, identifying gaps and creating new service offerings, and building corporate efficiencies for Advanced Clinical. She has spent much of her time over the past two years on decentralized trial strategy and approach and serves as a member of the Leadership Council for the Decentralized Trials & Research Alliance (DTRA). Caroline was the co-lead on the DCT evidence workstream with DTRA and led a site budgeting for DCTs workstream for ACRP.

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